REMARKS

Claims 1, 4-9, 52-55, 57, and 59-84 will be pending and under consideration upon entry of the above-made amendments. By these amendments, claims 3, 56 and 58 have been canceled without prejudice. Claims 1, 4-9, 52-53, 57, 59-66 and 69-71 have been amended to clarify that which Applicants regard as the invention. New claims 82-84 have been added. Applicants maintain the right to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications. The amended and new claims are fully supported by the specification as indicated below. No new matter has been added.

Claims 1, 53 and 57 are amended to recite that said lyophilate is made by a method comprising lyophilizing a composition lacking liposomes, and that said lyophilate has the ability to form liposomes of submicron size upon reconstitution with aqueous solution. Claims 1 and 57 are also amended to delete the phrase "submicron reconstitute" which is now redundant in light of the present amendments to these claims.

Claims 1 and 53 are further amended to recite that said lyophilate comprises both a non-lipid surfactant and a lipid.

Claim 53 is further amended to replace the term "average diameter" with the term "median diameter" to describe the size distribution of the liposomes produced upon reconstitution of said lyophilate.

Claim 57 is further amended to replace the term "solution" in steps (a) and (b) with the term "composition" in order to avoid confusion with the term "aqueous solution" as recited in this claim.

Claims 4-9 and 52, which depend from claim 1, are amended to delete the phrase "submicron reconstitute."

Claims 4 and 8 are further amended to no longer depend from cancelled claim 3, and to depend instead from presently pending claim 1.

Claims 59-65 are amended to replace the term "product" with the term "lyophilate" so as to be consistent with the language of presently amended claim 57.

Claims 59 and 64 are further amended to no longer depend from cancelled claim 58, and to depend instead from presently pending claim 57.

Claim 66 is amended to recite that said lyophilate was made by a method

comprising lyophilizing a composition lacking liposomes and to more clearly indicate that the non-lipid surfactant and not a lipid is present in an amount less than 4 mole % of the lipid content of said lyophilate. Claim 66 is also amended to replace the term "average diameter" with the term "median diameter" to describe the size distribution of the liposomes produced upon reconstitution of said lyophilate.

Claims 5, 60 and 69 are amended to replace the trademarked name "Tween" with it's appropriate chemical name "polyoxyethylene sorbitan carboxylate."

Claims 6, 61 and 70 are amended to replace the trademarked name "Tween 20" with it's appropriate chemical name "polyoxyethylene sorbitan monolaurate."

Claims 62 and 71 are amended to replace the trademarked name "Tween 80" with it's appropriate chemical name "polyoxyethylene sorbitan monooleate."

Support for Amended and New Claims

Support for the amended claims and for new claims 82-84 is found in the specification, for example, as set forth in the table below (citations being to the page and line numbers of the instant application).

Claim No.	Support
1	Page 5, lines 10-12; page 8, lines 24-25, page 10, lines 24-27; and page 11, lines 3 and 14-17
4, 8, 9, 52	Presently amended Claim 1
5, 60, 69	Page 32, lines 27-29
6, 61, 70	Page 12, lines 4-5
7, 62, 71, 82	Page 12, line 6
53	Page 11, lines 3 and 14-17
57	Page 10, line 27; page 11, lines 8-9 and 11-14
59, 61, 62, 64	Claim 57
63	Claims 57, 61 and 62
65	Claims 57 and 64
66	Page 4, lines 27-28 and page 11, lines 3 and 14-17

83	Page 4, lines 27-29 and page 5, line 4
84	Page 5, lines 4-12; page 10, lines 19-21

Interview Summary

Applicant and Applicants' representatives wish to thank Examiner Gollamudi S. Kishore for the interview conducted March 13, 2003 at the Patent Office and for the interview summary which was provided to Applicants' representatives at the conclusion of the interview. Present at the interview were Examiner Kishore, Applicants' representatives Adriane M. Antler and Jeffrey P. Bergman, and inventors Dr. Yiyu Zou and Dr. Roman Perez-Soler. During the interview, the instant application and proposed amendments thereto were discussed.

The proposed set of amended claims was discussed and Examiner Kishore suggested that the claims recite that the preliposome lyophilate does not contain liposomes at the time of lyophilization. The Examiner then commented on the applicants' proposal that the claims be amended to recite that the preliposome lyophilate provides liposomes of submicron diameter upon reconstitution, by noting that the phrase "submicron-reconstitute" as recited in numerous claims would be rendered redundant in light of the proposed amendment and suggested that this phrase be deleted. The Examiner further suggested that the trademarked surfactant names "Tween," "Tween 20" and "Tween 80" be deleted throughout the claims and replaced with their respective chemical names[1].

The Examiner then reviewed proposed claim 66 and suggested: (1) replacing the term "comprising" with the phrase "consisting essentially of"; (2) reciting a bioactive agent; and (3) reciting a lower limit for the range of surfactant. Attorney Antler respectfully disagreed with these proposed amendments and asserted that by amending claim 66 to replace the term "comprising" with the phrase "consisting essentially of," and to recite a bioactive agent, claim 66 would be limited only to lyophilates which contain a bioactive agent. Attorney Antler explained to the Examiner that a bioactive agent is not necessary since claim 66 is directed toward the preliposomal lyophilate, and not the liposome produced

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[1] Applicants have adopted these suggestions and have amended the claims accordingly.

upon reconstitution. Moreover, inventors Dr. Yiyu Zou and Dr. Roman Perez-Soler then explained how the liposomes which result from these lyophilates would have utilities other than as carriers for a bioactive agent that would be apparent to the skilled scientist and how an empty liposome could be of value. The rejection of claim 66 in the instant Office Action under 35 U.S.C. § 102 was then discussed and Applicants' representatives pointed out that the proposed amendments to claim 66 make it clear that a surfactant must be present and that the phrase "4% or less" as applies to the amount of surfactant present, could not be interpreted to have a lower limit of zero and thus, there is a finite lower limit already present for the surfactant in claim 66. In response, the Examiner stated that presently amended claim 66 "looks allowable," subject to a subsequent review of the art.

Attorney Antler then addressed the restriction requirement of the office action and the withdrawal of product-by-process claims 57-65 and the Examiner stated that if claim 66 was deemed allowable, he would consider rejoining the product-by-process claims.

Finally, inventors and applicants' representatives discussed why the instantly claimed invention was not made obvious by the prior art relied upon by the Examiner in the office action by pointing out that none of the cited references, individually or in combination, disclosed or suggested a lyophilate comprising lipid and surfactant, said lyophilate: (a) not having liposomes at the time of lyophilization; and (b) having the ability to form liposomes of submicron diameter upon reconstitution in aqueous media. The Examiner conditionally agreed that the instant invention is not obvious in light of the cited references, individually or in combination, but requested that applicants provide an explanation as to why the lyophilate described in Example 10 of U.S. Patent No. 5,585,112 to Unger et al. ("Unger") comprises surfactant but does not provide submicron diameter liposomes upon reconstitution in aqueous solution.

At the conclusion of the interview and prior to preparing the official Interview Summary, the Examiner agreed that the rejections under 35 U.S.C. § 102 and § 112 were overcome by the proposed amendments and stated that any suggestions made by the Examiner during the interview were "just suggestions" and are not absolute.

Additional details of Applicants' remarks in support of patentability are set forth below.

The Requirement For Restriction

In the Office Action dated July 12, 2002, new claims 57-65 were withdrawn from consideration. The Examiner asserts that the new claims were drawn to a distinct invention than that of the other claims since the new claims were drawn to a product produced by a specific process and that the lyophilate product does not contain liposomes, whereas the lyophilate of claim 1 need not be liposome-free. Applicants direct the Examiner's attention to claim 1 of the presently amended application. Claim 1 as presently amended, now recites that the lyophilate was made by lyophilizing a solution that did not comprise liposomes. Moreover, the instant specification, at page 11, lines 15-16, states that "[i]t is particularly to be understood that "preliposome-lyophilate" is not in liposomal form at the time of lyophilization." In light of the present amendments, Applicants believe that presently pending claims 57-65 should be rejoined and examined in the instant application.

Rejections Under 35 U.S.C. § 112

Claims 1 and 3-9 have been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Specifically, the Examiner contends that the phrase "preliposome-lyophilate comprising a non-lipid surfactant" is unclear as to whether the lyophilate contains only the surfactant, but no lipid. Applicants have amended claim 1 to clearly recite that the preliposome-lyophilate comprises both lipid and a non-lipid surfactant. Accordingly, the rejection of claims 1 and 3-9 under 35 U.S.C. § 112, second paragraph, has been overcome and the rejection should be withdrawn.

Claim 3 has been canceled without prejudice herein above, thereby rendering rejection of it moot.

Claims 66-81 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the phrase "about 4 mole % or less" as recited in claim 66 was deemed to be confusing as to whether this limitation applies to the surfactant or the lipid. Claim 66 is presently amended to clearly indicate that this limitation applies to the surfactant and not the lipid. In view of this amendment, the rejection of claims 66-81 under 35 U.S.C. § 112, second paragraph, has been overcome and the rejection should be withdrawn. Applicants also refer to the interview of March 13, 2003, in which the Examiner stated that in light of the present amendments, he would reconsider joining the product-by-process claims.

Rejections Under 35 U.S.C. § 102

Claims 66-67, 72-73 and 75 have been rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 4,950,432 to Mehta et al. ("Mehta I"). Mehta I discloses preliposomal powders containing a drug and a mixture of phospholipids, but no surfactant. The Examiner contends that the language "about 4 mole % or less" as recited in claim 66 could be construed as to pertain to the amount of surfactant present, and that the term "less" could have zero as a lower limit. Under these circumstances, the Examiner alleges that the preliposomal lyophilate of claim 66 could be interpreted as not having any surfactant present and is thus anticipated by Mehta I. Claim 66 has been presently amended to recite that the lyophilate comprises at least one lipid and a non-lipid surfactant and that the surfactant is present in an amount less than 4 mole % of the lipid content of the lyophilate. Applicants believe that this language makes it clear that: (a) the limitation applies to the surfactant and not the lipid, and (b) a surfactant must be present, thus making it clear that the term "less" as used in claim 66, is not to be interpreted as having a lower limit of zero. Thus, the present amendment overcomes the rejection of claims 66-67, 72-73 and 75 under 35 U.S.C. § 102(b), and the rejection should be withdrawn.

Claims 66-67 and 72 have been rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,811,119 to Mehta et al. ("Mehta II"). Mehta II discloses preliposomal powders containing retinoic acid and a mixture of phospholipids, but no surfactant. As discussed above, the Examiner contends that due to the allegedly confusing phrase "about 4 mole % or less," these claims could be interpreted as having no requirement for the surfactant and are thus anticipated by Mehta II. Accordingly, Applicants believe that the present amendment to claim 66 as stated above also overcomes the rejection of claims 66-67 and 72 under 35 U.S.C. § 102(e) and the rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1, 3-9, 52-56 and 66-81 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mehta I or Mehta II, further in view of Unger, U.S. Patent No. 5,089,602 to Isliker ("Isliker"), or U.S. Patent No. 5,653,996 to Hsu et al ("Hsu"), individually or in combination.

Claims 3 and 56 have been canceled without prejudice herein above, thereby rendering rejection of these claims moot.

Applicants respectfully disagree with the Examiner's rejection. To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). Secondly, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *M.P.E.P. 2143.* As detailed below, there is no suggestion or motivation either in the references cited by the Examiner themselves or in the knowledge generally available to one of ordinary skill in the art to modify the references or to combine the teachings of the references to arrive at the presently claimed invention. In addition, none of the references cited by the Examiner, individually or in combination, teach or suggest all the claim limitations.

None of the references cited by the Examiner disclose or suggest a lyophilate with lipid and surfactant, which lyophilate was made by lyophilizing a composition that did not contain any liposomes at the time of lyophilization, but which produces a submicron distribution of liposomes upon reconstitution. In contrast, the prior art references teach that to achieve a lyophilate that produces a submicron distribution of liposomes upon reconstitution, one first had to make liposomes, then use physical sizing methods (e.g., filter extrusion under pressure) to achieve a submicron size distribution of the liposomes, and then lyophilize. The claimed lyophilate differs in composition from these prior art lyophilates because no liposomes were present at the time of lyophilization, and was achieved based upon the inventors' discovery that the use of surfactant as taught in the instant specification unexpectedly allows the skilled artisan to achieve liposomes of submicron distribution without having first to make liposomes and then to size them. This is explained in more detail below with respect to the references cited by the Examiner.

Both Mehta I and Mehta II fail to teach liposomes of submicron distribution, much less a lyophilate, not made from liposomes, that provides the same. See e.g., Mehta II at col. 8, lines 19-21, which discloses a larger size distribution. Both Mehta I and Mehta II also fail to teach the use of a non-lipid surfactant in a lyophilate that lacked any liposomes at the time of lyophilization (or in any lyophilate).

Unger is concerned with gaseous precursor-filled liposomes. Unger teaches the use of physical sizing means exerted on liposome preparations to achieve submicron distributions of liposomes, and contains no hint or suggestion of a lyophilate, not made from

liposomes, that provides a submicron distribution. See e.g. Examples 14 and 15 (col. 45, line 29 to col. 46, line 7) of Unger, wherein liposomal suspensions are extruded under pressure through a membrane or passed through a microfluidizer in order to generate submicron size distributions. Although Unger does disclose the use of non-ionic surfactants to increase stability of the gaseous precursor-filled liposomes (col. 25, lines 38-48), and the use of emulsifying agents (col. 23, lines 20-47), Unger does not teach that surfactants can be used to achieve a submicron distribution of liposomes in the absence of physical sizing methods conducted upon liposomes, and thus does not hint or suggest a lyophilate which provides a submicron distribution upon reconstitution but which differs in composition from the prior art lyophilates since it did not contain liposomes at the time of lyophilization.

Regarding Unger's use of the surfactant sodium lauryl sulfate ("SLS") in Example 10 of Unger, during the interview the Examiner had suggested that applicants explain why the lyophilate described in Example 10 of Unger (at column 43, lines 45-67 and column 44, lines 1-9) comprises surfactant but does not provide submicron diameter liposomes upon reconstitution in saline. As is well-known in the art, SLS is an anionic detergent having a very large hydrophilic-lipophilic balance ("HLB") of approximately 40. See W. C. Griffin, *J. Soc. Cosmet. Chem.*, 1954, 5, 249-256 ("Griffin") (reference C14 in the Supplemental Information Disclosure Statement submitted herewith), at page 255, Table 1, last entry. The HLB value of a surfactant is an empirical expression for the relationship of the hydrophilic and hydrophobic properties of a surfactant and the HLB system is known to be useful to identify surfactants for aqueous emulsifications. In general, the higher the HLB value, the more hydrophilic (i.e., water-soluble) the surfactant. For a general discussion of the concept of HLB, see Shinoda et al., "Concept of Hydrophile-Lipophile Balance, HLB, of Surfactant" in *Emulsions and Solublization*, John Wiley and Sons, New York, NY (1986) ("Shinoda") (reference C15 in the Supplemental Information Disclosure Statement submitted herewith), at pages 55-93. Applicants explain that, as would be known by one skilled in the art in view of the teachings of the instant specification, in order to achieve submicron diameter liposomes upon reconstitution in aqueous solution, the surface energy of the water must be effectively reduced by the surfactant in order to allow said liposomes to be dispersed in the aqueous phase and form a very stable emulsion (e.g., an oil-in-water type emulsion). As indicated in Shinoda at page 68, Table 5, the ideal HLB range of a surfactant being used to form an oil-in water type emulsion is 8-18. In other words, the surfactant should have a

balance between its hydrophilic and lipophilic moieties such that it possesses good solubility in both the aqueous and non-aqueous (i.e. liposome) phases of the emulsion. The skilled artisan would recognize that SLS, as indicated by its very high HLB value of approximately 40 (which is the highest HLB value of any surfactant in the comprehensive list presented in Table 1 of Griffin and far outside the range listed in Shinoda for forming oil-in-water type emulsions), is almost completely water soluble, and thus the skilled artisan would not be motivated to use SLS as a surfactant for an application whose goal is the formation of a stable oil-in-water type emulsion of the type that would be necessary to provide small liposomes. As stated in Griffin at page 249, paragraph 3, lines 1-6:

> "Any emulsion chemist who works with surfactants for a few years soon recognizes that there is a correlation between their behavior and their solubility in water. For example, he will use a water-soluble surfactant or blend to make an oil-in-water emulsion. He will also use a water-soluble surfactant for solubilization and an almost completely water-soluble surfactant as a detergent."

It is well-known in the relevant art that SLS is typically employed as a detergent (not an emulsifying agent) in formulations such as laundry detergents, industrial cleaners, soaps and shampoos. Accordingly, based upon the very high HLB value of SLS and upon it's historical use as a detergent as opposed to an emulsifying agent, the skilled artisan would not have been motivated by the teachings of Unger (or in general) to use SLS in an application whose goal was to produce submicron diameter liposomes similar to those of the instant application, nor would one of skill in the art expect to achieve submicron liposomes using SLS in such an application. Instead, the skilled artisan would recognize that in order for the lyophilate described in Example 10 of Unger to provide small liposomes upon reconstitution, a surfactant having a lower HLB value than SLS should be used.

In addition, Example 10 of Unger uses DPPC (dipalmitoylphosphatidyl choline), which is a neutral lipid and, as such, liposomes that consist only of DPPC will possess no surface charge and be more prone to aggregation (and thus less prone to providing a submicron distribution) than liposomes comprised of a charged lipid. As stated in Borisov et al., "Stabilization of Colloidal Dispersions by Grafted Polymers" in Stealth Liposomes, Eds. D. Lasic and F. Martin, CRC press, New York, NY (1995) ("Borisov") (reference C16 in the Supplemental Information Disclosure Statement submitted herewith), at page 25,

paragraph 2, lines 1-4:

> "Colloidal dispersions are fundamentally unstable. Colloidal particles in suspension attract each other by the ubiquitious van der Waals forces. If this attraction is not counterbalanced by any repulsive force spontaneous aggregation of the particles occurs and the system flocculates."

Borisov at page 26, paragraph 2, lines 1-3 further states:

> "One of the first ways to ensure stability of colloidal suspensions in water is provided by the Coulomb repulsion between electrostatic charges which may be present on the particle surfaces."

Isliker also does not remedy the deficiencies of the above-discussed references, since Isliker also does not teach a submicron distribution of liposomes achieved without physical sizing of liposomes, and thus also does not suggest a submicron reconstitute lyophilate that did not contain liposomes at the time of lyophilization.

Isliker is directed toward a process for the isolation of apolipoproteins from blood plasma. The apolipoproteins can be put in proteoliposomes (col. 5, lines 12-16) and are used for treatment of cardiovascular disease (col. 5, lines 65-68). While Isliker does disclose the use of surfactants for the deaggregation or solubilization of lipoprotein aggregates during purification (col. 3, lines 28-34; col.4, lines 58-64), Isliker neither teaches nor suggests a lyophilate which does not contain surfactant at the time of lyophilization. Moreover, Isliker teaches the removal of surfactant prior to lyophilization (see col. 4, lines 61-64 and col. 8, lines 47-51). Therefore, Isliker does not cure the deficiencies of Mehta I or Mehta II, alone or in combination with Unger, since Isliker teaches neither a lyophilate which is free of liposomes at the time of lyophilization, nor a lyophilate which even contains surfactant.

Hsu teaches methods for the preparation of liposomes utilizing the aerosolization of a solution comprising bilayer forming materials and optional additional molecules onto an aqueous surface. While Hsu discloses the use of surfactants in making liposomes, Hsu does not teach that surfactants can be used to achieve a submicron distribution of liposomes in the absence of physical sizing methods conducted upon liposomes, and thus does not hint or suggest a lyophilate which produces a submicron

distribution upon reconstitution but which differs in composition from the prior art lyophilates since it did not contain liposomes at the time of lyophilization. In contrast, Hsu teaches physical sizing methods conducted upon liposomes in order to achieve submicron distribution (see col. 11, line 43 to col. 12, line 3). Thus, Applicants contend that the present invention is not obvious over Mehta I or Mehta II in light of Hsu, alone or in combination with the other cited references. Further, the Hsu reference was discussed during the interview and Examiner Kishore agreed with Applicants' interpretation of Hsu, stating that he did not feel that Hsu, alone or in combination with Mehta I or Mehta II would make the presently pending claims unallowable.

In view of the foregoing, Applicants respectfully assert that the rejection of claims 1, 3-9, 52-56 and 66-81 under 35 U.S.C. § 103(a) is in error and respectfully request that it be withdrawn.

CONCLUSION

Applicants respectfully request that the present amendment and remarks be entered and made of record in the instant application. It is submitted that all the outstanding rejections have been obviated or overcome. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: August 8, 2003

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Enclosures